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Author(s): L. J. WHITE, Y. H. SCHUKKEN, T. J. G. M. LAM, G. F. MEDLEY and M. J. CHAPPELL

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A multispecies model for the transmission and control of mastitis in dairy cows

L. J. WHITE¹*, Y. H. SCHUKKEN², T. J. G. M. LAM³, G. F. MEDLEY¹
AND M. J. CHAPPELL⁴

¹ Department of Biological Sciences, University of Warwick, Coventry CV4 7AL, UK

² Quality Milk Production Service, College of Veterinary Medicine, Cornell University, Ithaca, New York, USA

³ DeGraafshap Veterinary Services, HetHage 9 7251 XT Vorden, The Netherlands

⁴ School of Engineering, University of Warwick, Coventry CV4 7AL, UK

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SUMMARY

Mastitis in dairy cows is a significant economic and animal welfare issue in the dairy industry. The bacterial pathogens responsible for infection of the mammary gland may be split into two main categories: major and minor pathogens. Infection with major pathogens generally results in clinical illness or strong inflammatory responses and reduced milk yields, whereas minor pathogen infection is usually subclinical. Previous investigations have considered the transmission of these pathogens independently. Experimental evidence has shown cross-protection between species of pathogens. In this study a mathematical model for the coupled transmission of major and minor pathogens along with their interaction via the host was developed in order to consider various methods for controlling the incidence of major pathogen infection. A stability analysis of the model equilibria provides explanations for observed phenomena and previous decoupled modelling results. This multispecies model structure has provided a basis for quantifying the extent of cross-protection between species and assessing possible control strategies against the disease.

INTRODUCTION

A mathematical model is developed and analysed for the transmission of the two classes of pathogens that cause mastitis (inflammation of the mammary gland) in dairy cows. The two classes represent major and minor pathogens. Major pathogens are defined as those pathogens that are most likely to precipitate clinical disease or strong inflammatory responses (high somatic cell counts in milk) and comprise *Staphylococcus aureus*, *Streptococcus uberis*, *Streptococcus dysgalactiae*, *Streptococcus agalactiae* (not found in the herd forming the source of the data analysed here) and coliforms. Minor pathogens are

defined as those pathogens that infect the mammary gland, causing moderately elevated somatic cell counts, but do not, in general, cause clinical signs. The minor pathogen class comprises the species *Corynebacterium bovis* and coagulase-negative Micrococcaceae.

Multi-strain or multi-species models for the transmission of infectious disease have become increasingly common [1, 2]. Mostly, such models have been produced for viral infections (for example see White et al. [3]) with the aim of theoretical analysis of the systems [1, 4] or the simulated reproduction of observed dynamical characteristics [5]. The model presented here is similar to that proposed by Lipsitch [6] for the transmission of bacterial pathogens (*Strep-*

* Author for correspondence.

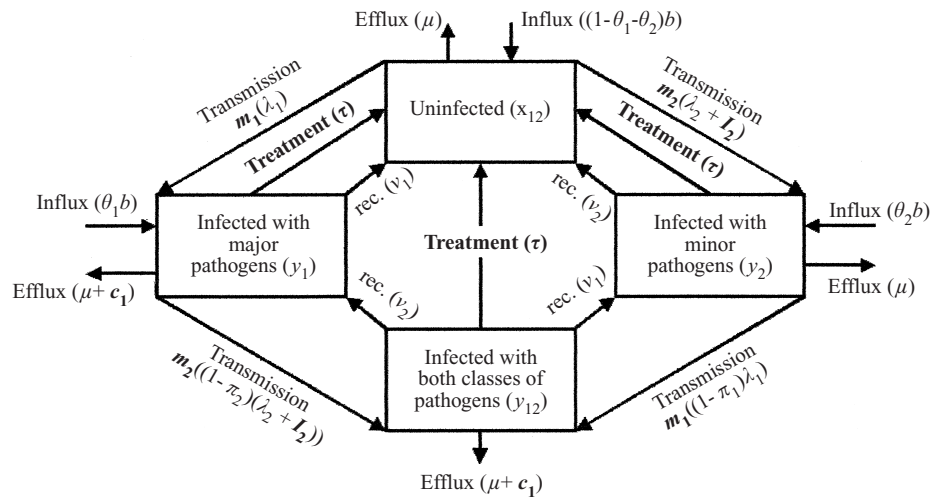


Fig. 1. A diagram of the multispecies model including controls (in bold).

Staphylococcus pneumoniae and *Haemophilus influenzae*) in humans, modified to apply to the transmission of mastitis in a herd of dairy cows. Previous applications have mostly been using vaccination as a method to reduce carrier status [6]. In the case of mastitis in dairy herds, vaccination is only one option, and treatment, culling, teat disinfection and possibly inoculation with benign strains are other options to consider.

Additionally, this paper extends the work of Lam et al. [7] on modelling mastitis transmission in cattle [where SIS (susceptible-infectious-susceptible) models were fitted to prevalence and incidence data from herds of dairy cows] that suggested some interaction in the transmission of the different pathogen species. During an outbreak of mastitis where minor and major pathogens were being transmitted, the basic reproduction number of *S. aureus* (a major pathogen) was shown to decrease during the course of the outbreak. This result has not been explained using the decoupled (no interaction between species) models. Our aim was to develop a simple multi-species model, where there is some cross-protection provided by infection by one class of pathogens (e.g. minor pathogens) against infection by another class (e.g. major pathogens) and examine the dynamic consequences of the interaction. The multispecies model is deterministic whereas the original SIS models were stochastic [7]. The model was then fitted by minimizing the deviation between the model output and the data.

The possible effects of controls imposed on systems of interacting strains of an infectious disease have been predicted using multistrain models [3, 4]. This work suggested that the traditional methods of control (e.g. strain specific vaccination) would not necessarily achieve the desired outcome (that is a reduction/

elimination of disease incidence). A number of possible controls against mastitis are considered using the multispecies model presented here. These controls take the form of those commonly used (postmilking teat disinfection, culling and treatment), alternatives (inoculation with minor pathogens) and combinations of these.

THE MODEL

Initially, it is assumed that hosts enter the system infected with major pathogens, minor pathogens or are uninfected in the respective proportions θ_1 , θ_2 , $(1 - \theta_1 - \theta_2)$. Infection with minor pathogens reduces the susceptibility of a host to major pathogens by a factor $(1 - \pi_1)$. Infection with major pathogens reduces the susceptibility of a host to minor pathogens by a factor $(1 - \pi_2)$. The basic force of infection of pathogen class i is given by λ_i day⁻¹. Because all the pathogens considered are assumed to be contagious, the force of infection depends on the proportion of infected animals and the transmission rate, β_i (proportion of infected hosts)⁻¹ day⁻¹. The spontaneous recovery rate of animals infected solely with pathogens of class i is ν_i day⁻¹. The culling rate for all cows is μ day⁻¹. Since herds are assumed to have a constant size, the influx rate, b day⁻¹, is assumed to be equal to the culling rate. The state variables x_{12} , y_1 , y_2 and y_{12} represent proportions of the total number of quarters in the herd which have respectively no infection, infection of major pathogens only, infection of minor pathogens only, and infection of both classes of pathogen. Figure 1 is a conceptual diagram of the system. The model structure presented here has the same structure as that proposed for the transmission

of bacteria causing pneumonia in human hosts [6], with the exception that it is possible for hosts to enter the system already infected with pathogens from either class, as it is possible for infected cows to be brought into a herd.

The equations describing the system are given by the following system.

$$\left. \begin{aligned} \dot{x}_{12} &= (1 - \theta_1 - \theta_2)b - (\lambda_1 + \lambda_2 + \mu)x_{12} + \nu_1 y_1 + \nu_2 y_2 \\ \dot{y}_1 &= \theta_1 b + \lambda_1 x_{12} + \nu_2 y_{12} - ((1 - \pi_2)\lambda_2 + \nu_1 + \mu)y_1 \\ \dot{y}_2 &= \theta_2 b + \lambda_2 x_{12} + \nu_1 y_{12} - ((1 - \pi_1)\lambda_1 + \nu_2 + \mu)y_2 \\ \dot{y}_{12} &= (1 - \pi_1)\lambda_1 y_2 + (1 - \pi_2)\lambda_2 y_1 - (\nu_1 + \nu_2 + \mu)y_{12} \\ b &= \mu \\ \lambda_1 &= \beta_1(y_1 + y_{12}) \\ \lambda_2 &= \beta_2(y_2 + y_{12}). \end{aligned} \right\} \quad (1)$$

This is a set of nonlinear ordinary differential equations where the interaction between the classes of pathogens via the host is quantified by the parameters π_1 and π_2 . The parameter π_1 denotes the level of cross-protection against major pathogens conferred during an infection of minor pathogens and vice versa for π_2 .

EXPLAINING OBSERVED PHENOMENA

The models considered by Lam et al. [7, 8] dealt with the transmission of pathogens of both classes separately and estimated key parameter values such as the basic reproduction number and average duration of infection. Although the basic reproduction number of minor pathogens did not vary significantly with time, the basic reproduction number for major pathogens decreased during an outbreak.

The method used by Lam et al. [7] for evaluating the basic reproduction number (\hat{R}_{0i}) of a pathogen was to estimate the transmission rate, $\hat{\beta}_i$, from the rate of new infections, K . The rate of new infections of major pathogens was defined as the product of the transmission rate, the proportion of the herd infectious with the pathogen, and the proportion of the herd susceptible to that pathogen. This is expressed in terms of the multispecies model state variables in eqn (1) as a constant ($\hat{\beta}_1$) multiplied by the product of the proportions of cows susceptible to major pathogens ($x_{12} + y_2$) and cows infected with major pathogens ($y_1 + y_{12}$), i.e.

$$K = \hat{\beta}_1(y_1 + y_{12})(x_{12} + y_2). \quad (2)$$

However, the multispecies model itself predicts that the rate of new infections of major pathogens would be the sum of the major pathogen transmissions rates

from the susceptible state, x_{12} , and the minor pathogen only infected state, y_2 [see eqn (1)]:

$$K = \beta_1(y_1 + y_{12})(x_{12} + (1 - \pi_1)y_2). \quad (3)$$

When eqns (2) and (3) are combined and rearranged, the following formula for the basic reproduction number as estimated by Lam et al. (\hat{R}_{01}) is given as a function of the state variables (x_{12} , y_1 , y_2 and y_{12}) and the major pathogen class basic reproduction number (R_{01}) of the multispecies model.

$$\left. \begin{aligned} \hat{R}_{01}(t) &= \frac{R_{01}(x_{12}(t) + (1 - \pi_1)y_2(t))}{(x_{12}(t) + y_2(t))}, \\ R_{0i} &= \frac{\beta_i}{\mu + \nu_i} \quad i \in \{1, 2\}. \end{aligned} \right\} \quad (4)$$

As can be seen from eqn (4), if there is no cross-protection during minor pathogen infection against infection by major pathogens (i.e. $\pi_1 = 0$), the basic reproduction numbers (from Lam et al. and the multispecies model) have the same value. If π_1 is greater than zero (i.e. there is cross-protection), the multispecies model predicts that the basic reproduction number for major pathogens as estimated by Lam et al. would vary in time. To consider the behaviour at the beginning of an outbreak, the derivative of \hat{R}_{01} with respect to time was calculated. A decrease in the basic reproduction number as estimated by Lam et al. would be indicated if its derivative is negative. The conditions at the beginning of an outbreak could be approximated by

$$x(0) = \begin{pmatrix} x_{12}(0) \\ y_1(0) \\ y_2(0) \\ y_{12}(0) \end{pmatrix} = \begin{pmatrix} 1 \\ 0 \\ 0 \\ 0 \end{pmatrix}. \quad (5)$$

The derivative of \hat{R}_{01} with respect to time at the beginning of an outbreak is given by

$$\left. \frac{d\hat{R}_{01}}{dt} \right|_{x(0)} = -\theta_2 \mu \pi_1 R_{01}, \quad (6)$$

which is strictly negative because the parameters θ_1 , μ and π_1 are all strictly positive. Therefore the multispecies model predicts that the basic reproduction number for major pathogens, as calculated by Lam et al. would decrease at the beginning of an outbreak, provided that $\pi_1 > 0$.

Figure 2 shows a fit of the multispecies model [eqn (1)] to the data analysed by Lam et al. [7] using the computer program Berkeley Madonna [9] which minimized the deviation between the model output

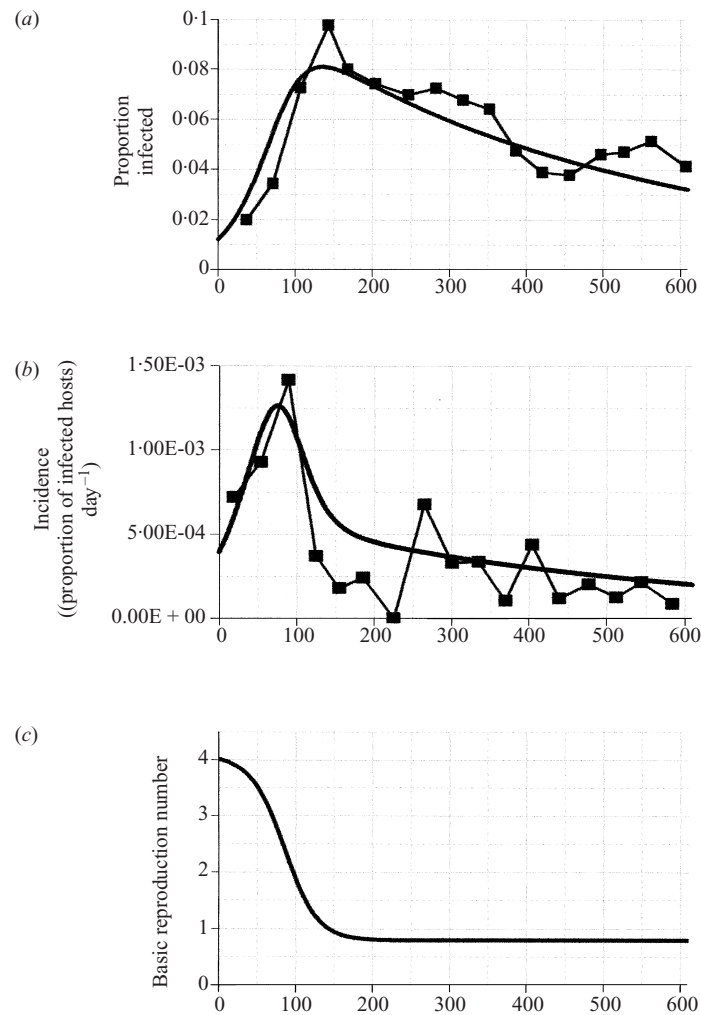


Fig. 2. Plots of the numerical solution of the multispecies model [eqn (1)] with parameter values: $R_{01} = 4.0$, $R_{02} = 12.0$, $\nu_1 = 0.0083 \text{ day}^{-1}$, $\nu_2 = 0.004 \text{ day}^{-1}$, $\mu = 0.0 \text{ day}^{-1}$, $\pi_1 = 0.87$ and $\pi_2 = 1.7 \times 10^{-4}$ and initial conditions: $x_{12}(0) = 0.982$, $y_1(0) = 4.1 \times 10^{-9}$, $y_2(0) = 0.0060$, $y_{12}(0) = 0.012$. Graph (a) shows the model output for the prevalence of *S. aureus* ($y_1 + y_{12}$) along with the corresponding data. Graph (b) shows the model output for the incidence of *S. aureus* [K , eqn (3)] along with the corresponding data. Graph (c) shows the value of the basic reproduction number for major pathogens as calculated from eqn (4) changing in time as the outbreak progresses.

and the data by varying the unknown parameter values. The minimization algorithm used was the ‘downhill simplex’ method described in [10]. The average duration minor pathogen infection assumed to be 250 days [8] then $\nu_2 = 0.04$. Influx and efflux was approximated by zero as it was assumed that little turn over of the herd would have taken place in the 18 months of the study period then $\mu = 0.0$. The initial conditions and all the other parameters were fitted. Figure 2(a) plots the proportion of the herd infected with *S. aureus* from the field study along with the corresponding model output ($y_1 + y_{12}$). Figure 2(b) plots the per teat incidence of *S. aureus* from the field study along with the corresponding model output, K , given by eqn (3).

Figure 2(c) plots the value for \hat{R}_{01} [basic reproduction number as calculated by Lam et al., eqn (4)] changing over time. It rapidly decays from the ‘outbreak’ value of approximately 4 to a ‘steady state’ value of around 0.8 over the first 200 days. This mimics the behaviour described by Lam et al. [7] where the outbreak values for the basic reproduction number for control and disinfected teats were estimated as 7.55 and 1.41 respectively with their steady state counterparts being 1.09 and 0.27. Because the multispecies model does not include postmilking teat disinfection for half the teats (as there was in the original herd), the fact that its estimates for the basic reproduction number lie between the control and disinfected estimates mentioned earlier provides

further validation of the model structure. This result clearly shows the influence minor pathogens would have on the transmission of major pathogens if some cross-protection against major pathogen infection is conferred during infection by minor pathogens ($\pi_1 > 0$).

Note that $d\hat{R}_{01}/dt$ was calculated for a specific condition of the system [eqn (5)] and the derivative [eqn (6)] would not always be negative, depending on the values of the state variables (i.e. the instantaneous condition of the system) when the basic reproduction number, \hat{R}_{01} , is calculated.

INVASION OF MAJOR PATHOGENS

It can be assumed that in certain circumstances θ_1 is zero because animals infected with major pathogens may be prevented from entering the herd.

For $\theta_1 = 0$, expressions for the minor pathogen only equilibrium values of the state variables (x_{12}^* , y_1^* , y_2^* and y_{12}^*) in terms of the parameters are given by

$$\left. \begin{aligned} x_{12}^* &= \frac{R_{02} + 1 - \sqrt{(R_{02} - 1)^2 + \frac{4R_{02}\mu\theta_2}{(\mu + \nu_2)}}}{2R_{02}}, \\ y_2^* &= \frac{R_{02} - 1 + \sqrt{(R_{02} - 1)^2 + \frac{4R_{02}\mu\theta_2}{(\mu + \nu_2)}}}{2R_{02}}, \end{aligned} \right\} \quad (7)$$

where

$$\left. \begin{aligned} R_{01} &= \frac{\beta_1}{(\mu + \nu_1)}, \\ R_{02} &= \frac{\beta_2}{(\mu + \nu_2)}. \end{aligned} \right\} \quad (8)$$

The basic reproduction numbers [R_{01} and R_{02} for major and minor pathogens respectively in eqn (8)] are defined as the number of hosts infected by a single infectious host entering a completely susceptible (to both classes of pathogen) host population, that is where no cows enter the herd already infected. Major and minor pathogens can coexist if each class can invade the population when the other class is present at equilibrium [6], and therefore major pathogens are competitively excluded if eqn (9) is satisfied,

$$R_{01}(x_{12}^* + (1 - \pi_1)y_2^*) < 1, \quad (9)$$

that is

$$R_{01} < \frac{R_{02}}{R_{02} - \frac{\pi_1}{2} \left[R_{02} - 1 + \sqrt{(R_{02} - 1)^2 + \frac{4R_{02}\mu\theta_2}{(\mu + \nu_2)}} \right]}. \quad (10)$$

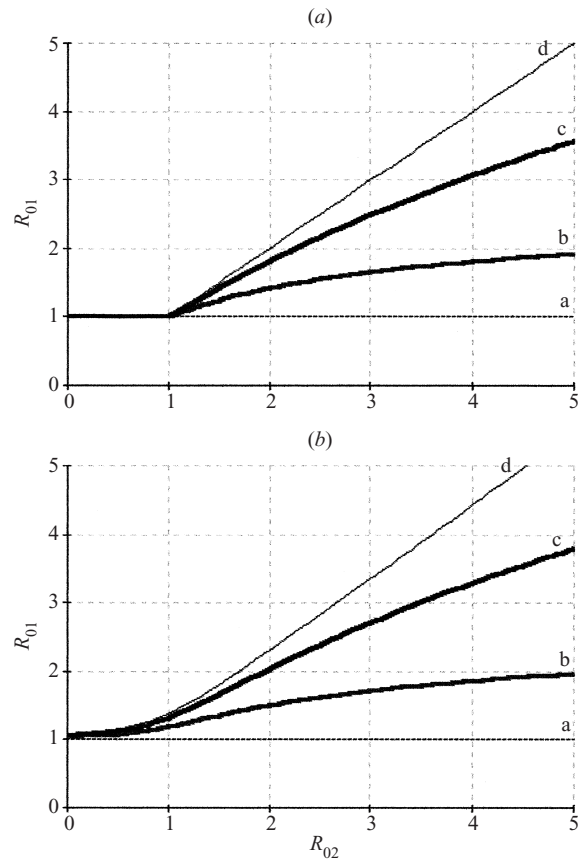


Fig. 3. Graphs showing the boundary in (R_{02}, R_{01}) -space between where the coexistence equilibrium is stable (above the line) and where the minor-pathogen-only equilibrium is stable (below the line). The effects of cross-protection of minor infections against major infections, π_1 , and proportion of animals entering the herd already infected with minor pathogens, θ_2 , on the boundary are shown. Line a, $\pi_1 = 0$; line b, $\pi_1 = 0.6$; line c, $\pi_1 = 0.9$; line d, $\pi_1 = 1$. Graph (a) $\theta_2 = 0$, graph (b) $\theta_2 = 0.5$.

Figure 3 shows the boundary in parameter space between where the minor pathogen only equilibrium is stable and where it is unstable (and therefore the equilibrium where both major and minor pathogen classes are present is stable). It also shows how this boundary is affected by changes in the level of cross-protection of minor pathogen infections against major pathogen infections, π_1 , and the influx of minor pathogen infectives into the herd, θ_2 . Any value of the pair (R_{01}, R_{02}) which is placed below the curve for a particular value of π_1 will result in only minor pathogen infection persisting in the herd. Any value of the pair (R_{01}, R_{02}) which is placed above the curve for a particular value of π_1 will result in the invasion/persistence of major pathogen infections. Because the major pathogen infections can cause clinical illness, it

is desirable to maintain a parameter set, or impose a control that results in the competitive exclusion of major pathogen infections. Although derived from equations describing a different mechanism for cross-protection between interacting species, the shape of the resulting graph is very similar to those produced from other modelling work related to the competition between strains or species of pathogens [3, 11, 12].

CONTROL

The model [eqn (1)] was adapted to include control strategies in the form of postmilking teat disinfection, antibiotic treatment, culling of infected animals and inoculation of animals with minor pathogens.

Postmilking teat disinfection has been shown to have the effect of decreasing the transmission rate (of *S. aureus*) by a factor of the order of 10^{-1} [7]. This effect is included in the model in the form of two parameters. The parameters m_1 and m_2 represent the multiplicative decreases in the transmission rates of major and minor pathogens respectively. Treatment is modelled in the form of a density dependent flow rate, τ , from all the infectious classes (y_1 , y_2 and y_{12}) to the susceptible compartment (x_{12}). The initial estimate for the parameter value for τ is 0.01 day^{-1} . This is based on a mean time to detection of 60 days, and an estimated cure rate after treatment of 60% [13]. This would represent a realistic but aggressive treatment policy. Culling is modelled as an additional density dependent mortality rate, c_1 , from the major pathogen infected compartments (y_1 and y_{12}). An initial estimate for the parameter c_1 is 0.017 day^{-1} . This is based on a mean time to detection of 60 days. Animals would be immediately culled after detection, a very restrictive and expensive management policy. Inoculation of animals with minor pathogens is modelled as an additional force of infection, I_2 . Eqns (11) and (12) show the extended multispecies model with controls included.

$$\left. \begin{aligned} \dot{x}_{12} &= (1 - \theta_1 - \theta_2)b - (m_1\lambda_1 + m_2\lambda_2 + \mu)x_{12} + (\nu_1 + \tau)y_1 + (\nu_2 + \tau)y_2 + \tau y_{12}, \\ \dot{y}_1 &= \theta_1 b + m_1\lambda_1 x_{12} + \nu_2 y_{12} - ((1 - \pi_2)m_2\lambda_2 + \nu_1 + \mu + c_1 + \tau)y_1, \\ \dot{y}_2 &= \theta_2 b + m_2\lambda_2 x_{12} + \nu_1 y_{12} - ((1 - \pi_1)m_1\lambda_1 + \nu_2 + \mu + \tau)y_2, \\ \dot{y}_{12} &= (1 - \pi_1)m_1\lambda_1 y_2 + (1 - \pi_2)m_2\lambda_2 y_1 - (\nu_1 + \nu_2 + \mu + c_1 + \tau)y_{12}, \end{aligned} \right\} \quad (11)$$

where

$$\left. \begin{aligned} 1 &= x_{12} + y_1 + y_2 + y_{12}, \\ b &= \mu + c_1(y_1 + y_{12}), \\ \lambda_1 &= \beta_1(y_1 + y_{12}), \\ \lambda_2 &= \beta_2(y_2 + y_{12}) + I_2. \end{aligned} \right\} \quad (12)$$

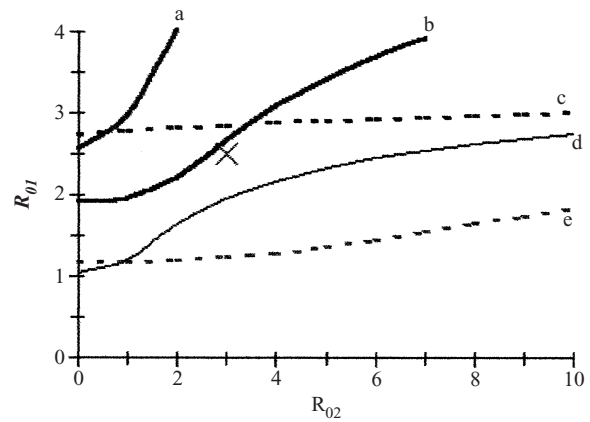


Fig. 4. A graph showing the boundary in (R_{02}, R_{01}) -space between where the coexistence equilibrium is stable (above the line) and where the minor-pathogen-only equilibrium is stable (below the line). Line d shows the boundary for the parameter set $\theta_1 = 0.0$, $\theta_2 = 0.5$, $\nu_1 = \nu_2 = 0.01 \text{ day}^{-1}$, $\mu = 0.0015 \text{ day}^{-1}$, $\pi_1 = 0.7$ and $\pi_2 = 0.0$ where the model includes no controls (i.e. $\tau = c_1 = I_2 = 0 \text{ day}^{-1}$ and $m_1 = m_2 = 1$). Line b, treatment (at rate $\tau = 0.01 \text{ day}^{-1}$). Line a, culling of major pathogen infected cows (at rate $c_1 = 0.017 \text{ day}^{-1}$). Line e, postmilking teat disinfection (with parameters $m_1 = 0.9$ and $m_2 = 0.2$). Line c, inoculation of cows with minor pathogens (at rate $I_2 = 0.1 \text{ day}^{-1}$).

The cross-protection curve is plotted, in Figure 4, showing the changes in the boundary between the stability of the coexistence versus the minor-pathogen-only equilibria effected by the various control strategies.

Line d of the graph in Figure 4 shows the starting point of the comparison, where no controls are in place. The cross indicates a particular uncontrolled system with reasonable values for the basic reproduction numbers for major and minor pathogens ($R_{01} = 3$, $R_{02} = 2.5$). The cross is above the line implying that major pathogens should be able to invade the system and persist at equilibrium.

When treatment is included in the model, the

boundary is shifted upwards, therefore decreasing the likelihood of invasion of major pathogens into the herd. In the example illustrated by Figure 4, the treatment cure rate was high enough to move the

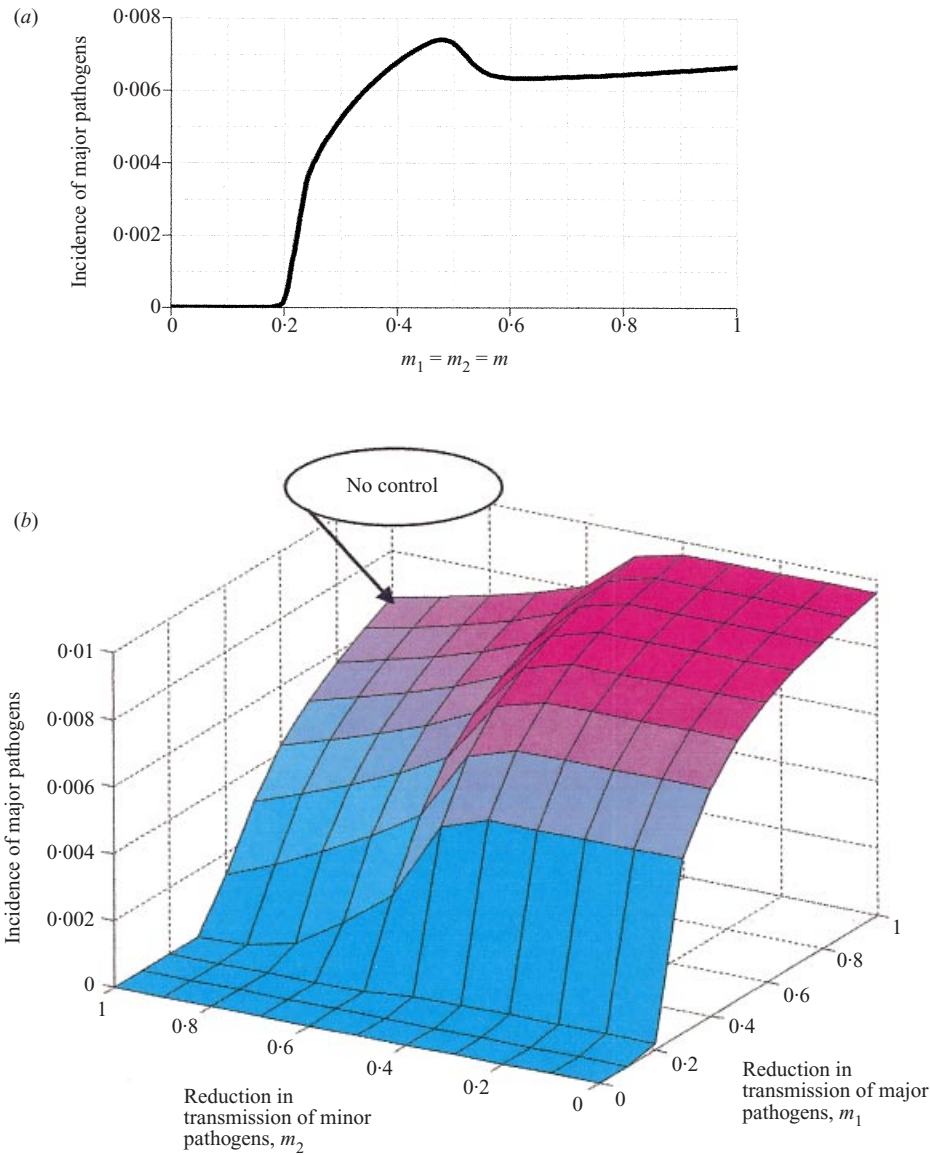


Fig. 5. Graphs showing the incidence of major pathogens at equilibrium (vertical axis), for the parameter set $\beta_1 = 0.07 \text{ day}^{-1}$, $\beta_2 = 0.03 \text{ day}^{-1}$, $\theta_1 = 0.0$, $\theta_2 = 0.0$, $\nu_1 = \nu_2 = 0.01 \text{ day}^{-1}$, $\mu = 0.0015 \text{ day}^{-1}$, $\pi_1 = 0.85$ and $\pi_2 = 0.0$. (a) The transmission of major and minor pathogens are affected to the same extent by postmilking teat disinfection (i.e. $m = m_1 = m_2$). (b) The transmission of major and minor pathogens can be affected to different extents by postmilking teat disinfection. That is, the equilibrium incidence of major pathogens is plotted for values of m_1 and m_2 from zero to unity. The graph allows a comparison of different effects of postmilking teat disinfection with the natural state (i.e. $m_1 = m_2 = 1$) and thus incorporates graph (a).

boundary above the cross and would therefore successfully eliminate major pathogens from the herd. The culling of cows infected with major pathogens (at the same rate as the treatment cure rate) had a more pronounced effect, moving the boundary much higher for increasing values of R_{02} .

Postmilking teat disinfection, having the effect of reducing the transmission of both classes of pathogen, changes the position of the boundary in a more complicated way. Decreasing the transmission of the

major pathogen classes (by a factor m_1) moves the boundary upwards. Decreasing the transmission of the minor pathogen classes (by a factor m_2) decreases the curvature of the boundary. Then it is possible to have a situation (for $m_1 > m_2$) where the overall effect is that parts of the boundary are lower than they were without postmilking teat disinfection. This situation is illustrated in Figure 4 with line e and, in this case, the control would fail and possibly increase the incidence of major pathogen infection in the herd.

To illustrate these effects, two graphs were plotted (Fig. 5). The two-dimensional graph shows how, for a particular parameter set, the incidence of major pathogens at equilibrium increases before it decreases as the effects of postmilking teat disinfection increase (i.e. as $m = m_1 = m_2$ decreases). The three-dimensional graph shows the effects of varying m_1 and m_2 independently of each other. It can be clearly seen that parts of the surface (indicating the incidence of major pathogens at equilibrium) are higher than the region that relates to the absence of postmilking teat disinfection [i.e. at $(m_1, m_2) = (1, 1)$].

Inoculation of the cows with minor pathogens has the effect of moving the part of the boundary for lower values of R_{02} upwards. There would therefore only be a significant effect if the cross-protection curve was steep. This is the case when there is a high level of cross-protection of minor pathogen infection against major pathogen infections (π_1). Line c in Figure 4 shows this control as effective for a high value (0.7) for π_1 .

DISCUSSION AND CONCLUSIONS

We have developed a transmission dynamic model of mastitis infection in dairy cows that considers both major and minor pathogens. Within the context of the model we can explain the observed [7] reduction in basic reproduction number for major pathogens (during an outbreak of both major and minor pathogens) as a consequence of cross-protection conferred by infection with minor pathogens. This protection most likely acts through enhanced (non-specific) immunity in the udder [8], although direct competition has also been reported [14]. The latter mechanism is very similar to the one proposed by Lipsitch [6] with regard to nasopharyngeal infections with *Haemophilus influenza* and *Streptococcus pneumoniae* in humans. Proposed biological phenomena behind direct competition include toxin production (i.e. lysostaphin), competition for nutrients or competition for receptors [8, 14].

We have demonstrated from the model predictions that ecological interactions between pathogen species (and strains) can have important influences on transmission dynamics, and that competition between species may be an important control option with regard to the transmission of clinically important pathogens [3, 15]. Such interactions can greatly enhance or reduce the effect of efficient control measures [3, 4, 15].

The equilibrium results presented here are similar to those of O'Callaghan et al. [16], in which disease (due to *Cowdria ruminantium*) can be increased by a reduction in transmission (*Amblyomma* attachment rate): a concept termed endemic stability in the tick-borne disease literature [17]. Essentially, only very intense control measures (elimination of both major and minor pathogens in the current context) are able to reduce disease below levels which pertain when no control is operating.

We have extended the modelling of Lam et al. [7, 8, 18–20], on the transmission of mastitis pathogens as well as providing some validation of a standard multispecies model structure [6]. The model also permits an explanation for the drop in basic reproduction number reported by Lam et al. [7]. Other factors (such as specific immunity, segregation or partial segregation of clinically ill cows and selection of less susceptible cows or quarters) may influence the basic reproduction number during an outbreak of major pathogens. However, the multispecies model presented here shows that competition between major and minor pathogens (via co-infection) alone can account for this phenomenon. The incorporation of multiple interacting species or strains into deterministic rather than stochastic structures [1–6] has been performed possibly because deterministic modelling techniques are more readily applied to such high order nonlinear systems. In this case, the deterministic model reproduced the previously observed drop in basic reproduction number of major pathogens whilst providing an accompanying explanation related to the interaction of minor and major pathogens. Future work would include the development and fit of the stochastic counterpart of the multispecies model, therefore allowing a direct comparison with its single species predecessor [7].

Steady state analysis has produced a 'cross-protection curve' (Fig. 3) that has a similar form to those produced from other multistrain/species models [3, 11, 12]. A similar analysis on the model equations extended to include various control procedures has given some theoretical insight into their possible effects.

It was predicted that postmilking teat disinfection (the intervention that had an effect on the transmission of both minor and major pathogens) entailed some risk of increasing the likelihood of major pathogen outbreaks. This control strategy could, in some cases, reduce the amount of minor pathogen infection and therefore the extent of competitive exclusion of major

pathogens. There is a trade-off between the reduction of the transmission of major pathogens and the reduced cross-protection against major pathogen infections provided by minor pathogen infections. This analysis has particular significance because postmilking teat disinfection is a commonly used method. Barkema et al. [21] observed that approximately 60% of Dutch dairy farms were practicing postmilking teat disinfection. Evidence already exists that casts doubt on the efficacy of postmilking teat disinfection in the prevention of *Escherichia coli* (a coliform, major pathogen) [20]. Infections with *Escherichia coli* usually originate from the environment and are not prevented by teat disinfection. This would translate in the model to a value close to 1 for the parameter m_1 , whereas m_2 would be much closer to 0.

Controls acting only on major pathogens, like the culling of diseased animals (i.e. those infected with major pathogens) and antibiotic treatment, were shown to reduce the risk of major pathogen outbreaks. This is frequently practised by dairy farmers, and probably leads to short term success. However, long term, continuous high culling rates are not feasible in the current economic climate and are also an unattractive solution with regard to animal welfare.

Inoculation of cows with minor pathogen species would enhance the herd immunity against major pathogen infections. However, there must be a sufficiently high level of natural cross-protection against major pathogen infection provided by infection with the minor pathogens for them to out-compete the major pathogens. Although a theoretically feasible option, it is not logistically easy to infect animals with minor pathogens without, at the same time, increasing the risk of coinfection with major pathogens. Novel application systems would need to be developed to make this a feasible option.

Controls acting on a heterogeneous system are difficult to predict [3, 4, 6, 22] and care should be taken to ensure that an intervention does not perturb the balance between competing organisms in a way that offsets the benefit of control. Instead, ideally, controls should enhance the competitive exclusion of pathogens causing clinical disease. Different control strategies give quite different profiles for the cross-protection curve and, in some cases, a combination of different strategies could be the optimal way to reduce the occurrence of clinical mastitis. Finding an optimal combination of control procedures within the model is the subject of current study.

The multispecies model presented could be used to design effective control strategies if its parameters were identified with sufficient precision and then used in conjunction with appropriate field testing of the proposed strategies. The dynamical output of the model is consistent with the data from the biological system. It is important to note that the fit presented here has resulted in estimates of a large number of parameters using only two time series. It is an example of how the model can reproduce observed behaviour and a complete fit would require further data. Future work involves the fitting of the basic model to prevalence and incidence data and then using the framework to design effective control strategies. This process could be repeated for models (of increased complexity) that include more detail concerning the transmission mechanisms for the pathogens, the demographics of the herd and economics of production. Further validation/development of the model structure, in the form of specifically designed experiments, would increase the accuracy of the modelling results. Although the work presented here pertains specifically to the pathogens that cause mastitis in dairy cows, the same techniques of model development, analysis and application to data can be applied to other groups, species, or strains in other host populations.

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